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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/889,203	03/13/2002	Tracey Brown	229752005700	8511

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EXAMINER	
FUBARA, BLESSING M	
ART UNIT	**PAPER NUMBER**
1618	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/889,203	BROWN, TRACEY	
	Examiner	Art Unit	
	BLESSING M. FUBARA	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27,30,32,33,36,38,39,42,44,45,48,50-52 and 57-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27,30,32,33,36,38,39,42,44,45,48,50-52 and 57-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/22/09; 10/05/09; 8/17/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Examiner acknowledges receipt of request for extension of time, request for continued examination under 37 CFR 1.114, amendment to the claims and specification and remarks filed 8/17/09. The examiner also acknowledges receipt of IDS filed 10/22/09, 10/05/09, and 8/17/09. The examiner further acknowledges receipt of power of attorney filed 6/03/09. Claims 27, 30, 22, 33, 36, 38, 39, 42, 44, 45, 48, 50 and 51 are amended. Claims 28, 29, 31, 34, 35, 37, 40, 41, 43, 46, 47, 49 and 53-56 are canceled. New claims 57-62 are added. Claims 27, 30, 32, 33, 36, 38, 39, 42, 44, 45, 48, 50-52 and 57-62 are pending.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/17/09 has been entered.

Response to Arguments

Previous rejections that are not reiterated herein are withdrawn.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 27, 30, 32, 33, 36, 38, 39, 42, 44, 45, 48, 50-52, 57, 58 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over della Valle et al. (US 5,442,053).

4. Claims 27, 33, 39, 45 and 51 have been amended to limit the molecular weight of the hyaluronan to 890,000 Da.

5. della Valle describes an embodiment in which a pharmaceutical composition comprising active agents and hyaluronic acid as the carrier vehicle (abstract) for administration in various forms (column 3, lines 60 and 61; column 5, line 60; column 14, line 13; column 16, lines 38-46; column17, line 11). The cytotoxic agents named in della Valle are fluorouracil, methotrexate and podophyllin (column 24, lines 65 and 66) meeting the requirement for chemotherapeutic agents of claims 27, 32, 33, 38, 39, 44, 45, 50 and 51. The method of enhancing the efficacy of the chemotherapeutic agent in claims 27 and 33, the method of overcoming acquired resistance of cancer cells to chemotherapeutic agents in claim 39 comprises systemic administration of effective amount of hyaluronan and chemotherapeutic agent to a subject in need thereof. Thus, the contemplation by della Valle to administer the composition systemically (see column 17, line 48) meets the mode of administration such that the effect of the composition after administration, that is, enhancing the efficacy of the chemotherapeutic agent in claims 27 and 33, the method of overcoming acquired resistance of cancer cells to chemotherapeutic agents in claim 39 are met. The polydispersity of the hyaluronan recited in claims 57, 58 and 61 are the properties of the hyaluronan so that the hyaluronan of della Valle having that intrinsic property meets the requirements of claims 57, 58 and 61.

6. della Valle does not use hyaluronic acid having molecular weight of 890,000 as recited in generic claims 27, 33, 39 and 51 and dependent claims 30, 36, 42, 48 and 52. However, the

disclosure to use hyaluronan having a range of molecular weight or from about 500,000 to about 730,000 Da (claims 5, 8, 18 and 32), and the general teaching that as a vehicle, hyaluronic acid of varying molecular weights can be used (column 18, lines 63-66) and that the molecular weight of HA is generally up to about 8-13 million, suggest that although, molecular weight in the range of about 500,000 to 730,000 Da may be used, hyaluronic acid of other molecular weight may also be used including hyaluronic acid of molecular weight higher than 730,000 Da being mindful of the intrinsic viscosity of the hyaluronic acid carrier vehicle (column 4, lines 13-23). Therefore, taking the general teaching of della Valle, the person of ordinary skill in the art at the time the invention was made would have reasonable expectation of success that using hyaluronic acid having molecular weights in a range that is higher than the 730,000 Da that results in a carrier vehicle having desired viscosity would provide the anticipated therapeutic composition for successful delivery of cytotoxic agents.

Response to Arguments

7. Applicant's arguments filed 8/17/09 have been fully considered but they are not persuasive.

8. Applicant argues that della Valle does not teach intravenous systemic administration. The examiner agrees that della Valle does not teach intravenous administration as recited in claims 59 and 60. The examiner notes that the present rejection does not include claims 59 and 60 that are specific to intravenous administration. Further, although, claim 62 is a composition claim and the route of administration is the intended use of the composition using the administration route, this claim also is not included in the current rejection over della Valle. However, intravenous administration is not the only systemic route of administration. For example enteral and parenteral administrations are also systemic. Enteral administration includes

oral, rectal, and sublingual administrations. Parenteral administration includes piercing the skin or mucous membrane. Specifically, della Valle contemplates administering the composition systemically (see column 17, line 48), which meets the systemic mode of administration of the claims. Therefore, della Valle teaches systemic administrations.

9. Applicant argues that della Valle does not teach the molecular weight of 890,000 Da. The examiner also agrees with the applicant that della Valle does not teach the 890,000 and that is why the rejection is not anticipatory. But there is a suggestion that HA having molecular weight other than 730,000 Da can be used as described in the rejections above so that it would have been obvious to use HA having higher molecular weight greater than 730,000 Da that is expected to having the desired viscosity and the anticipated therapeutic composition for successful delivery of cytotoxic agents.

10. Claims 27, 30, 32, 33, 36, 38, 39, 42, 44, 45, 48, 50-52 and 57-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Falk et al. (US 5,985,850).

11. Falk discloses injectable formulations comprising anti-cancer agent or chemotherapeutic agent and hyaluronic acid (column 10, lines 8-59). The preferred molecular weight for the hyaluronan is less than 750,000 Daltons (claims 142, 83, 84 and 92). The anti-cancer drug or chemotherapeutic agent of Falk, specifically, methotrexate and 5-fluorouracil (claims 38 and 79) meet the chemotherapeutic agents of claims 27, 32, 33, 38, 39, 44, 45, 50 and 51. The method of enhancing the efficacy of the chemotherapeutic agent in claims 27 and 33, the method of overcoming acquired resistance of cancer cells to chemotherapeutic agents in claim 39 comprises systemic administration of effective amount of hyaluronan and chemotherapeutic agent to a subject in need thereof. Falk's method of administration of the hyaluronan containing composition is by intravenous, intra arterially, intraperitoneally, intrapleurally, transdermally,

topically, rectally, or by direct injection of the of the composition into a tumor (column 10, lines 48-55), which meets the mode of administration of the claims such that the effect of the composition after administration, that is, enhancing the efficacy of the chemotherapeutic agent in claims 27 and 33, the method of overcoming acquired resistance of cancer cells to chemotherapeutic agents in claim 39 are met. Furthermore, the intravenous administration contemplated by Falk meets the requirements of claims 59 and 60 and because the composition is contemplated for intravenous administration, the requirements of claim 62 is met even as a composition claim in which the route of administration would not patentably distinguish the composition over the composition of the prior art. The polydispersity of the hyaluronan recited in claims 57, 58 and 61 are the properties of the hyaluronan so that the hyaluronan of Falk having that intrinsic property meets the requirements of claims 57, 58 and 61

Falk does not use hyaluronic acid having molecular weight of 890,000 as recited in generic claims 27, 33, 39 and 51 and dependent claims 30, 36, 42, 48 and 52. However, Falk contemplates the use of HA having higher molecular weight and the requirement is that the composition be diluted to permit administration that does not coagulate (column 19, lines 32-34) and specifically HA having molecular weight in the range of 750,000 to 1,200,000 is suggested (column 18, lines 64, 65). Therefore, taking the general teaching suggestion of Falk, the person of ordinary skill in the art at the time the invention was made would have reasonable expectation of success that using hyaluronic acid having molecular weights in a range of 750,000 to 1,200,000 and using the appropriate dilution to provide a composition having a viscosity such that the composition does not coagulate, would be suitable carrier vehicle having desired viscosity that would provide the anticipated therapeutic composition for successful systemic delivery of cytotoxic agents. A molecular weight of 890,000 Da lies within the suggested range

of 750,000 to 1,200,000 Da so that the molecular weight of 890,000 Da in generic claims 27, 33, 39 and 51 and dependent claims 30, 36, 42, 48 and 52 would be obvious.

Response to Arguments

12. Applicant's arguments filed 8/17/2009 as the arguments apply to the current rejections under 35 USC have been fully considered but they are not persuasive.

13. Applicant argues that Falk does not teach molecular weight of 890,000 Da and that when Falk suggests the use of HA having higher molecular weight, the composition having the higher molecular weight HA is for topical application for ocular, intra-articular and skin wounds; that nothing in Falk would lead the skilled artisan to predict the enhanced efficacy of systemically administered HA having modal molecular weight of 890,000 Da.

14. The examiner disagrees. The rejection is not an anticipatory rejection. Falk teaches the anticancer agents of the claims; Falk teaches HA in combination with the anticancer agent and suggests that HA having molecular weight within the range of 750,000 to 1,200,000 Da can be used with a further suggestion to dilute such a composition to avoid coagulation. The second paragraph (column 19, lines 40-43) after the suggestion to use HA having molecular weight, Falk talks about obtaining unexpected results from the combination of HA and therapeutic agents. Therefore, taking the teaching of Falk, the skilled artisan would be led to using HA having molecular weight within the range of 750,000 to 1,200,000 Da. Applicant obtains enhanced efficacy of chemotherapeutic agent by systemically administering composition that contains HA and therapeutic agent. In the same way, the systemic administration of composition comprising HA and therapeutic agent as contemplated by Falk would also enhance the efficacy of the chemotherapeutic agent.

15. Applicant states the declaration by Dr. Tracey Brown filed 9/11/06 shows that HA having molecular weight greater than 750,000 Da is superior to the HA of Falk. The declaration (filed 9/11/06) by Dr. Tracey Brown had been addressed in the office action of 10/30/2008 and will be addressed below. However, in paragraph 3, the declaration is comparing effect of HA on varying concentrations of 5-Fluorouracil and specifically uses 880,000 and 1,429,000 Da while the claims do not have drug concentrations and the molecular weight for the current claims is at 890,000 Da. In paragraph 4, the declaration compares the resistance of cancer cell to methotrexate and combination of HA and methotrexate, but the Falk reference teaches combination of HA and methotrexate. On the whole, because the claims have not recited amounts of the HA and the chemotherapeutic agent, the declaration using specific concentration of chemotherapeutic agents is not commensurate with the claims.

Declaration by Dr. Tracy Brown:

16. The declaration under 37 CFR 1.132 filed 8/19/08 is insufficient to overcome the rejection of claims 27, 30, 32, 33, 36, 38, 39, 42, 44, 45, 48, 50-52 and 57-62 based upon the rejection under 35 U.S.C. 103(a) as obvious over Falk et al. (US 5,985,850).35 U.S.C. 103(a) as set forth in the present office action because: The declaration in 1B uses molecular weight of about 150 kDa for the HA, 250, 400 and 700 kDa in Figs 2, while claims 27, 33, 39 and 39 use molecular weight of 890 kDa.

17. In paragraph 3, the declaration is comparing effect of HA on varying concentrations of 5-Fluorouracil and specifically uses 880,000 and 1,429,000 Da while the claims do not have drug concentrations and the molecular weight for the current claims is at 890,000 Da. In paragraph 4, the declaration compares the resistance of cancer cell to methotrexate and combination of HA and methotrexate, but the Falk reference teaches combination of HA and methotrexate. On the

whole, because the claims have not recited amounts of the HA and the chemotherapeutic agent, the declaration using specific concentration of chemotherapeutic agents is not commensurate with the claims.

18. Paragraphs 7 and 8 of the declaration do not use amounts of HA and drugs and it is not persuasive that compositions can be prepared without using any amounts and it is also not persuasive that a composition prepared by dumping together HA and drug in any amounts would provide the desired effect. If that were the case, then the declaration would also apply to the prior art.

19. The examiner agrees with paragraph 8 of the declaration that viscosity increases with molecular weight but the declaration, being an opinion declaration has not accounted for the effect of concentration on the viscosity. Regarding the phase I and II clinical trials presented in the declaration, it is noted that only the molecular weight of the HA and the drugs are named, there are no amounts/concentrations of HA or the drugs and it is fair to assume that data cannot be generated without specific concentrations of the HA and the drug because such a test would mean the dumping of any amount of HA and drug to form a composition that may provide any effect of any desired treatment, which by implication would cover the prior art.

20. No claim is allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BLESSING M. FUBARA whose telephone number is (571)272-0594. The examiner can normally be reached on 7 a.m. to 5:30 p.m. (Monday to Thursday).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 7571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Blessing M. Fubara/
Examiner, Art Unit 1618